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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/432,503	11/02/1999	THOMAS R. CECH	15389-002611	1130

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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 03/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/432,503	CECH, T. ETAL.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-62 and 65-82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *41-57 and 74-82* is/are allowed.

6)☒ Claim(s) *58-62 and 65-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 May 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/04;10/04;12/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Action is in response to the communication filed on 12/24/04. The amendment filed 12/24/04 is acknowledged. The amendment has been entered. Claims 41-62, 65-82 are currently pending in the application and are addressed herein.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on 8/23/2004, 10/08/2004, and 12/24/2004 are acknowledged. The submissions are in compliance with the provisions of 37 CFR 1.97. Accordingly, the Examiner has considered the information disclosure statements.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 58-62 and 65-73 are finally rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed methods of increasing the proliferative

capacity of a cell wherein the cell is in vitro, does not reasonably provide enablement for methods of increasing the proliferative capacity of a cell wherein the cell is in vivo, for the reasons of record set forth in the previous Office Action. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The rejection was set forth in the previous Office Action, and is reiterated below for convenience.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

Given the broadest reasonable interpretation, the nature of the invention is biomedical therapy and includes gene therapy for treating humans having disease or disorder.

The breadth of the claims

As indicated above, the claims are very broad and encompass methods for increasing the proliferative capacity of mammalian cell by administering to the cell a polynucleotide that encodes a polypeptide that has telomerase catalytic activity when complexed with a telomerase

RNA. A careful reading of the claim language also reveals that the claim does not explicitly require that the target mammalian cell have the Telomerase RNA required for TRT catalytic activity. Claims 58-91 encompass the method wherein the mammalian cell is in vivo. With respect to the in vivo embodiments of the claims, it is respectfully pointed out that the only contemplated use for the method described in the specification is for treating disease/disorder. As such, the only contemplated use for the method is for gene therapy to treat a disease/disorder. With respect to treating a disease/disorder, it is respectfully pointed out that the claims are not limited to treating any particular specific disease and the specification specifically contemplates treating a vast array of different diseases including: cancer, Alzheimer's disease, Parkinson's disease, stroke, graying of hair, hair loss, wound healing, osteoporosis, age-related immune system impairment, atherosclerosis, diabetes, muscle atrophy, etc. (e.g., see p. 98-100). Furthermore, the claims do not specifically indicate how the polynucleotide is delivered to the cells; therefore, the claims embrace any type of administration/delivery of the therapeutic molecule. Therefore, given the broadest reasonable interpretation of the claims, the claims encompass a method for treating any disease/disorder using the claimed method by any means of administration.

The unpredictability of the art and the state of the prior art

With respect to claims as they read on administering a polynucleotide comprising a sequence encoding a catalytically active TRT, one of skill in the art would be fully aware that in order for the polynucleotide to express the encoded polypeptide in a cell, the sequence encoding the polypeptide must be operably linked to transcriptional control elements (such as promoter/enhancer elements). If the polynucleotide sequence is not operably linked to

transcriptional control elements, then one of skill in the art would not expect the sequence to be expressed.

With respect to the claims as they encompass administering the polynucleotide to cells that do not comprise Telomerase RNA, it is respectfully pointed out that the specification indicates that the activity of TRT requires the presence of the Telomerase RNA (TR) to function as a template for initiating the catalytic activity of TRT. Therefore, one of skill in the art would recognize that in order for the claimed method to work, the target cell must comprise the required telomerase RNA.

With respect to the claims as they encompass in vivo embodiments (as indicated above) the claims encompass gene therapy for treating disease. Regarding gene therapy as a whole, the art at the time of filing considered gene therapy to be unpredictable as modes of delivery that would provide efficient expression of genes encoding the therapeutic polypeptide sufficient to provide an alleviation of symptoms related to the target disease or condition had not been developed. Currently, the state of the art of gene therapy is still in its infancy as the art is plagued by unpredictability. For instance, ANDERSON (Nature 392(Suppl):25-30; 1998) teaches,

> "Except for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene therapy protocol has been successful in the treatment of a human disease (p.25, first paragraph)... The challenge is to develop gene therapy as an efficient and safe drug-delivery system. The goal is more difficult to achieve than many investigators had predicted 5 years ago. (p. 25 , second paragraph)... Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered. The reason for the low efficiency of gene transfer and expression in human patients is that we still lack a basic understanding of how vectors should be constructed, what regulatory sequences are appropriate for which cell types, how in vivo immune defenses can be overcome and how to manufacture efficiently the vectors we do make."(See p. 30).

With respect to using TRT for gene therapy, the relevant art indicates that there are a number of problems that must be overcome in order for TRT gene therapy to be considered predictable. For instance, HORNSBY et al. (J. Anti-Aging Med, 2000) teaches,

> "The use of telomerized cells depends on expression of (hTRT) not causing changes that predispose cells to abnormalities of any kind, particularly neoplastic conversion. Since the initial reports of telomerization, conflicting data have been presented with respect to risks of abnormalities in cells that have been telomerized... The data that have been obtained so far do not unequivocally show the (hTRT) is able to immortalize cells without the production of any abnormalities... Other data, in fact, suggest that immortalization by (hTRT) could predispose cells to neoplastic transformation. Most significant is the finding that expression of (hTRT) is required for full tumorigenicity in human cells also expressing mutated Ras and large T/small t antigens from SV40... Considering the available data, we cannot yet predict whether telomerized cells transplanted into a host animal do in fact present a cancer risk; this can only be determined directly by long-term observation, and this has not yet been done." (See p. 412)

HORNSBY also teaches,

> "The future prospects for the use of telomerized cells are significant. As emphasized here, major efforts need to be made to be sure that telomerization is safe when applied to cells for use in human therapy." (See p.416)

OSTLER et al. (J. Ped. Endocrin. & Metab., 2000) teaches that telomerase (hTRT) has been shown to halt telomere shortening and is sufficient to prevent senescence in at least three human cell types (fibroblasts, vascular endothelial cells and retinal pigmented cells) conferring first extended life span and then formal immortality (e.g., see last paragraph p. 1472).

Regarding telomere-driven senescence mechanisms in other mammals, OSTLER teaches,

> "It is unlikely, however, that this [telomere-driven senescence] mechanism operated in rodent species. Rodents have much greater mean telomere lengths than humans, a significant spontaneous escape frequency from senescence (10-6/cell/generation compared with 10-12/cell/generation in humans) and (more seriously) some rodent fibroblasts have been shown to undergo senescence in the presence of active telomerase." (See p. 1473, first paragraph).

Regarding the possible use of Telomerase for therapeutic purposes, OSTLER teaches,

> "There is considerable popular interest in the potential application of telomerase to tissue engineering and anti-aging therapies. Leaving aside the practical difficulties of the safe use of telomerase, it is clear that ectopic expression of the enzyme (or even transient telomerase reactivation) should not be treated as a 'one size fits all' intervention for compromised replicative capacity in every tissue." (See p. 1474).

Therefore, it is clear that the relevant art recognizes that treating diseases that are contemplated by the specification is harder than merely increasing the proliferation of cells associated with the disease and a number of different factors have to also be considered and addressed before TRT gene therapy can be considered a predictable art.

Working Examples and Guidance in the Specification

The specification shows the nucleic acid (and amino acid) sequences that encode a few different TRT genes from different species, and indicates the potentially conserved homologous domains of the different TRTs (e.g., see Fig. 4). The specification also shows that expression of hTRT in different cells types, wherein the cells are in vitro (e.g., see Fig. 5 and Example 2). The specification also shows that the co-expression of hTRT and hTR are required for telomerase catalytic activity in a cell, in vitro (that is, both TRT and the Telomerase RNA are required) (e.g., see Fig. 10). The specification, however, does not have any working examples wherein the target cells are in vivo. Furthermore, the specification does not show how the polynucleotide encoding the TRT can be administered to the correct target cell in vivo, and how to avoid transformation of non-target cells in vivo. The specification does not indicate any specific functional variants or fragments of hTRT that can be used in the claimed method. The specification does disclose that deleting certain specific domains of the polypeptide eliminates the catalytic activity of the protein, but there is no evidence presented indicating that any specific

fragment or variant of hTRT (i.e. SEQ ID NO: 2) has catalytic activity when expressed in a cell. The specification also does not offer any guidance with respect to expressing the catalytic molecule in a cell wherein the polynucleotide encoding the catalytic molecule is not operably linked to expression control elements (such as in a vector).

Quantity of Experimentation

Considering the vast breadth of the claims, an enormous amount of additional experimentation would be required in order for one of skill in the art to be able to predictably use the claimed invention to its full scope. For instance, additional experimentation would be required in order to be able to use the claimed method to treat a mammal having a disease/disorder. Considering the problems recognized in the art at the time of filing and in the post-filing art (indicated above), it is clear that the additional experimentation would not be a matter of "routine experimentation". Furthermore, the evidence presented in the instant specification (e.g., see Fig 10) indicates that in order to produce a telomerase catalytic activity in a cell both the TRT and TR genes must be expressed in the cells (i.e., the cells must have both the telomerase enzyme and the telomerase RNA unit). However, the claims do not explicitly indicate that the target cell expresses both TRT and TR. Therefore, additional experimentation would be required in order to be able to practice the claimed method in a cell that does not express TR. Again, this would not be a matter of routine experimentation. Furthermore, the claims do not explicitly indicate that the polynucleotide encoding the telomerase polypeptide is operably linked to transcriptional control elements (such as a vector). Since one of skill in the art would be aware that this was required to properly express the recombinant gene in a cell, additional experimentation would be required.

Level of the skill in the art

The level of the skill in the art is deemed to be high, considering the complex nature of biomedical therapy.

Conclusion

Considering that the claims are extremely broad such that they encompass methods that can be performed either in vitro or in vivo, and considering that the in vivo embodiments of the claims encompass treating a vast number and different types of diseases wherein the mere increasing of the proliferation of the cells associated with the disease would not be expected to result in treatment of the disease, the claims are not enabled to the full scope that they embrace. That is, considering the nature of the invention (gene therapy) and the vast breadth of the claims (treating any disease via any type of administration) in view of the teaching in the art that gene therapy is unpredictable and in view of the limited working examples and guidance provided at the time filing, as well as the high degree of skill required to practice the claimed invention, it is concluded that the amount of experimentation required to perform the broadly claimed invention is undue.

Response to Amendment/Arguments

Applicant's arguments filed 12/24/04 have been fully considered.

With respect to the rejection of claims under 35 USC 112, 2nd paragraph, and 35 USC 112, 1st paragraph (written description rejection only). The amendment and/or arguments are persuasive and the rejections are withdrawn.

With respect to the rejection of claims under 35 USC 112, 1st paragraph (scope of enablement), Applicants arguments have been fully considered and the rejection of claims 41-57

has been withdrawn as the claims are drawn to cells in vitro only. However, Applicants arguments with respect to the in vivo method claims (claims 58-62 and 65-73) are not persuasive. Therefore, claims 58-62 and 65-73 are finally rejected for the reasons of record.

With respect to the rejection of claims 58-62 and 65-73, Applicants argue that claim 58 has been amended to refer to an adenoviral vector as a means for delivering the therapeutic TRT gene into a target cell and that claims 65-73recite particular cell types that that have been previously shown to be capable of transduction in vivo by an adenoviral vector.

Applicants' arguments have been fully considered but are not persuasive. First, it is respectfully pointed out that the Office did not indicate that amending the instant claims such that the claims were limited to an adenoviral vector would obviate the instant rejections. A copy of the interview summary is attached. In the personal interview of 9/1/2004, the breadth of the claims was discussed with respect to the broad range of vectors encompassed by the claims. It was note that not all vectors were known to transduce all cell types encompassed by the claims. It was suggested that Applicants consider limiting the claims to Adenoviral vector and the specific cell types that can be transduced by Adenoviral vectors in order to address the this particular issue only. Limiting the instant claims to the use of an adenoviral vector to deliver the TRT gene does not overcome the issues with respect to treating disorders in a subject, the only contemplated use found in the specification for the instant claimed method.

With respect to the instant rejection, as previously set forth, the claims are very broad and encompass methods for increasing the proliferative capacity of mammalian cell in vivo by administering to the cell a polynucleotide that encodes a polypeptide that has telomerase catalytic activity when complexed with a telomerase RNA. With respect to the in vivo

embodiments of the claims, it is respectfully pointed out that the only contemplated use for the method described in the specification is for treating disease/disorder. As such, the only contemplated use for the method is for gene therapy to treat a disease/disorder. With respect to treating a disease/disorder, it is respectfully pointed out that the claims are not limited to treating any particular specific disease and the specification specifically contemplates treating a vast array of different diseases including which includes treating cancer, Alzheimer's disease, Parkinson's disease, stroke, graying of hair, hair loss, wound healing, osteoporosis, age-related immune system impairment, atherosclerosis, diabetes, muscle atrophy, and diseases resulting from cell senescence (particularly diseases of aging), (e.g., see p. 98-100).

The specification, however, does not provide any working examples or any specific guidance that enables the treatment of any specific disorder. That is, the instant specification does not provide an enabling disclosure that would enable the treatment of any specific disease, including wound healing, as the specification does not sufficiently describe any specific method including the proper vectors as well as routes of administration, the particular type of wounds that can be treated, and the particular effects such a method on wound healing such that one of skill in the art would be able to practice the method for treating wounds. Applicants are respectfully reminded that the instant claims are not limited to treating wounds, and encompass treating a huge number of different disorders, as indicated above.

It is noted that a Declaration under 37 CFR 1.132 has been filed. The Declaration of Dr. Wirth has been considered by the Examiner. The Declaration under 37 CFR 1.132 filed 12/4/2004 is insufficient to overcome the rejection of claims 58-62 and 65-73 as set forth in the

last Office action. The Declaration of Dr. Wirth has been submitted with respect to the Examiner's position that the Rudolph et al. reference, which teaches increasing the proliferative capacity of mouse cells in vivo using a vector that expresses telomerase, is not a proper model for the instant claimed Invention.

The Declaration is not persuasive because the instant claims encompass a method of increasing the proliferative capacity of a cell in vivo. Looking to the specification for guidance, it appears that the only contemplated use for increasing the proliferative capacity of a cell in vivo

Is for treating a disease or disorder. Therefore, the only contemplated use for the instant claimed method is for gene therapy of a disorder. The animal model taught by Rudolph et al. is not an acceptable model because it teaches a transgenic animal wherein a specific gene has been knocked out, resulting in a particular phenotype (cirrhosis-like liver disease). Rudolph teaches that a vector which encodes the knocked-out gene (the RNA subunit of telomerase) can be administered to the affected liver cells and results in reduction of the diseased phenotype in the animal. However, such knock-out animal models wherein the knocked-out gene is reintroduced into the cell is not considered an acceptable model for gene therapy. Furthermore, the telomerase activity in the animal model is significantly different from the telomerase activity in humans (e.g., see the Table on page 3 of the Declaration). Furthermore, as previously indicated, the art (specifically OSTLER) teaches,

> "It is unlikely, however, that this [telomere-driven senescence] mechanism operated in rodent species. Rodents have much greater mean telomere lengths than humans, a significant spontaneous escape frequency from senescence (10-6/cell/generation compared with 10-12/cell/generation in humans) and (more seriously) some rodent fibroblasts have been shown to undergo senescence in the presence of active telomerase." (See p. 1473, first paragraph).

Thus indicating a significant difference between rodents and humans with respect to telomerase activity.

Therefore, the Declaration of Dr. Wirth is not persuasive with respect to the rejection of the instant claims.

Allowable Subject Matter

Claims 41-57 and 74-82 are allowed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon Eric Angell, Ph.D.
Art unit 1635

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PRIMARY EXAMINER